## Remarks

### I. Status of the Application and Claims

As originally filed, the present application had a total of 4 claims. These were cancelled in a Preliminary Amendment and new claims 5-24 were added. No claims were cancelled or added herein.

### II. The Amendments

No amendments have been made herein.

## The Rejections

The Examiner has maintained a rejection of all pending claims as being obvious over Dormoy, *et al*. (*Synthesis*, pg. 81-86 (1996)), in view of Carlsen, *et al.,* (*J. Org. Chem. 46*:3936-3938 (1981)) and Riley, *et al*. (*J. Chem. Soc., Chem. Commun*., 1530-1532 (1983)) and further in view of Narukawa, *et al*. (*Tetrahedron 53*:539-556 (1997)). Dormoy allegedly teaches the conversion of hydroxyprolines to ketoprolines using a ruthenium catalyst in a biphasic organic solvent system. Carlsen and Riley have been cited as teaching ruthenium catalyzed oxidations in solvent systems containing water and Narukawa as teaching that t-boc protected oxo-proline compounds are not very soluble in water.

Applicants respectfully traverse this rejection.

The Examiner has cited three references describing two phase reaction systems, Dormoy, Carlsen and Narukawa. Stabilization in these systems appears to be achieved by separating reaction components into different phases and not by crystallization. Nevertheless, the Examiner has asserted that it would have been obvious to replace the two phase system of these references with a one phase system and stabilize product by crystallization because: a) crystallization is routine in the art; b) the order in which reagents are added does not make an invention patentable; c) Riley suggests an oxidation system that has only one phase; and d) Narukawa suggests that ketoprolines are poorly soluble in aqueous media. Applicants respond to each of these allegations below.

**Allegation 1: Crystallization is Routine in the Art**

Applicants submit that the Examiner's assertion that crystallization procedures are routine in the art is irrelevant to the obviousness of the present claims. The fact that a purification procedure (*e.g.*, chromatography, ion exchange, etc.) is commonly used does not mean that its application to a particular problem involving compound stability is obvious. None of the references cited by the Examiner suggests stabilizing compounds by crystallization during oxidation reactions. Applicants also do not believe that crystallization according to the claimed process can reasonably be inferred based upon Riley teaching a one phase oxidation system and Narukawa teaching poor ketoproline solubility in aqueous solvents. These references are discussed further below.

**Allegation 2: Riley Suggests an Oxidation System That Has Only One Phase**

In previous prosecution, Applicants have pointed out that ketoprolines are not among the oxidation products considered by Riley and that it is not clear that stability problems of the same degree exist for the compounds studied in this reference. In addition, it appears that the products in Riley were analyzed directly in solution; they were not precipitated or crystallized (see footnote on page 1531).

The Examiner states that the "combined references suggest to one of ordinary skill to make the modifications necessary to practice the instant invention with a reasonable expectation of success." However, this statement is merely conclusory and fails to meet the requirement that Examiner's provide a logical basis for rejecting claims. Why would the combined references suggest crystallizing ketoprolines to stabilize them when none of the references include a crystallization step? Why would combining references that stabilize products by separation in a two phase system with a reference that does not stabilize products at all suggest using a one phase system in which products are stabilized by crystallization occurring concurrently with the addition of oxidizing agent? In the absence of an explanation as to how one gets from the cited references to the claimed invention, Applicants submit that the present rejection cannot be validly maintained.

**Allegation 3: Narukawa Suggests that Ketoprolines are Poorly Soluble in Aqueous Media**

Narukawa uses a two phase reaction system and purifies product by extraction. One of the products examined in the reference (compound 15) was a ketoproline. This was purified by extraction and found in the organic phase. This means that, under the conditions used in the extraction, the ketoproline was more soluble in the organic solvents used than in the aqueous solvent. It is not the same thing as teaching that the ketoproline is poorly soluble in aqueous solvents.

However, even accepting that one of skill in the art would know that ketoprolines are not very soluble in aqueous solvents, this does not make the use of crystallization during the addition of oxidizing agent to stabilize compounds in a one phase system obvious. Narukawa appears to have deliberately kept the ketoproline in solution; it does not report performing a crystallization as either a purification or stabilization step. This is also true of all of the other references cited.

**Allegation 4: The Order that Reagents are Added to a Reaction is Not a Basis for Patentability**

In previous prosecution, Applicants have argued that it is not just the crystallization of ketoproline product that is important to the claimed invention but also the timing of the crystallization. The compounds must be crystallized rapidly after they are made in order to prevent further oxidation steps. This is the reason that the claims require crystallization at the time that oxidizing agent is added.

In response, the Examiner has stated that the order of addition of reagents to a reaction is not a basis for patentability. However, Applicants have not just changed the order of reagent addition in the processes taught by the cited references. Crystallization during the addition of oxidizing agent to stabilize product is a concept that is entirely missing from the references either when considered alone or in combination. Moreover, the Examiner has not provided any rational basis on which this could be inferred.

## Conclusion

In light of the discussion above, Applicants respectfully submit that a prima facie case of obviousness has not established. It is therefore requested that the rejection of claims be withdrawn and that the present application be passed to allowance.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicants' undersigned attorney at (240)683-6165.

Respectfully submitted,

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